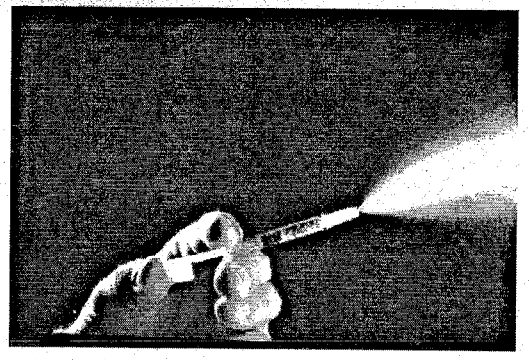
**Aviron**



**FluMist**

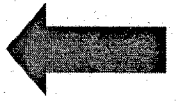
# An Influenza Vaccine For Use in Healthy Children Age 1 – 17

## Safety in Children

***Paul M. Mendelman, MD***
**Aviron**

# Historical Experience with CAIV Prior to Aviron Clinical Trials

| Population | Number Enrolled |
|---|---|
| Children<br>Adults | 2743<br>5348 |
| Total (All Ages) | 8091 |



- Primarily monovalent or bivalent formulations

**Conclusion: CAIV was safe and well-tolerated**

# Children Vaccinated with FluMist

## Aviron Experience

**Children All Studies**

| Age | Healthy | High Risk |
|---|---|---|
| 1 – 8 Years | 12069 | 777[a] |
| 9 – 17 Years | 6321 | 540[b] |
| Total | 18390 | 1317[c] |

[a] 23 with HIV infection vs. controls

[b] 24 with moderate to severe asthma vs. controls

[c] 1270 with a history of wheezing illness or mild asthma (Open Label Study)

**Conclusion: 19,707 children vaccinated with FluMist**

# Collection of Safety Data

Aviron Trials

- **Methods**
  - Diary card
  - Monitoring of medical records
  - Telephone calls to participants
  - HMO database review
- **Types**
  - Serious adverse events (Day 0 to Day 42)
  - Post-vaccination reactogenicity period (Day 0 to Day 10)
    - Reactogenicity events (pre-specified)
    - Other adverse events (not pre-specified)
    - Medication use

# Demographic Characteristics at Time of First Vaccination

Healthy Children Age 1-17

| Characteristic | 1 – 8 Years of Age | | 9 – 17 Years of Age | |
|---|---|---|---|---|
| | FluMist N = 11993 | Placebo N = 2792 | FluMist N = 6321 | Placebo N = 1359 |
| Age, Years | | | | |
| Median/Mean | 4 | 4 | 12 | 12 |
| Gender | | | | |
| Female | 51% | 51% | 51% | 50% |
| Race/Ethnicity | | | | |
| White | 62% | 60% | 65% | 59% |
| Hispanic | 17% | 17% | 18% | 18% |
| Black | 10% | 7% | 8% | 7% |
| Asian | 4% | 9% | 4% | 9% |
| Other | 7% | 7% | 4% | 6% |

# Serious Adverse Events In Children

Children Age 1-17

| Population | FluMist | Placebo |
|---|---|---|
| | # SAEs / # Enrolled (%) | # SAEs / # Enrolled (%) |
| 1 – 8 Years | | |
| Healthy | 51 / 12069 (0.4%) | 14 / 2805 (0.5%) |
| Asthma | 7 / 754 (1%) | 0 / 0 (0%) |
| HIV-infected | 2 / 23 (9%) | 1 / 24 (4%) |
| 9 – 17 Years | | |
| Healthy | 21 / 6321 (0.3%) | 1 / 1359 (0.1%) |
| Asthma | 2 / 540 (0.4%) | 0 / 24 (0%) |

Note: Does not include SAEs from ongoing Study AV018.

**Conclusion: The rates of SAEs were low.**

# Mortality in Children

Children Ages 1-17

- **Two Deaths**
  - One due to bronchopneumonia 27 days after Dose Two
    - Not vaccine related
  - One due to a posterior fossa tumor and malignant hyperthermia 145 days after dosing in a second season
    - Not vaccine related

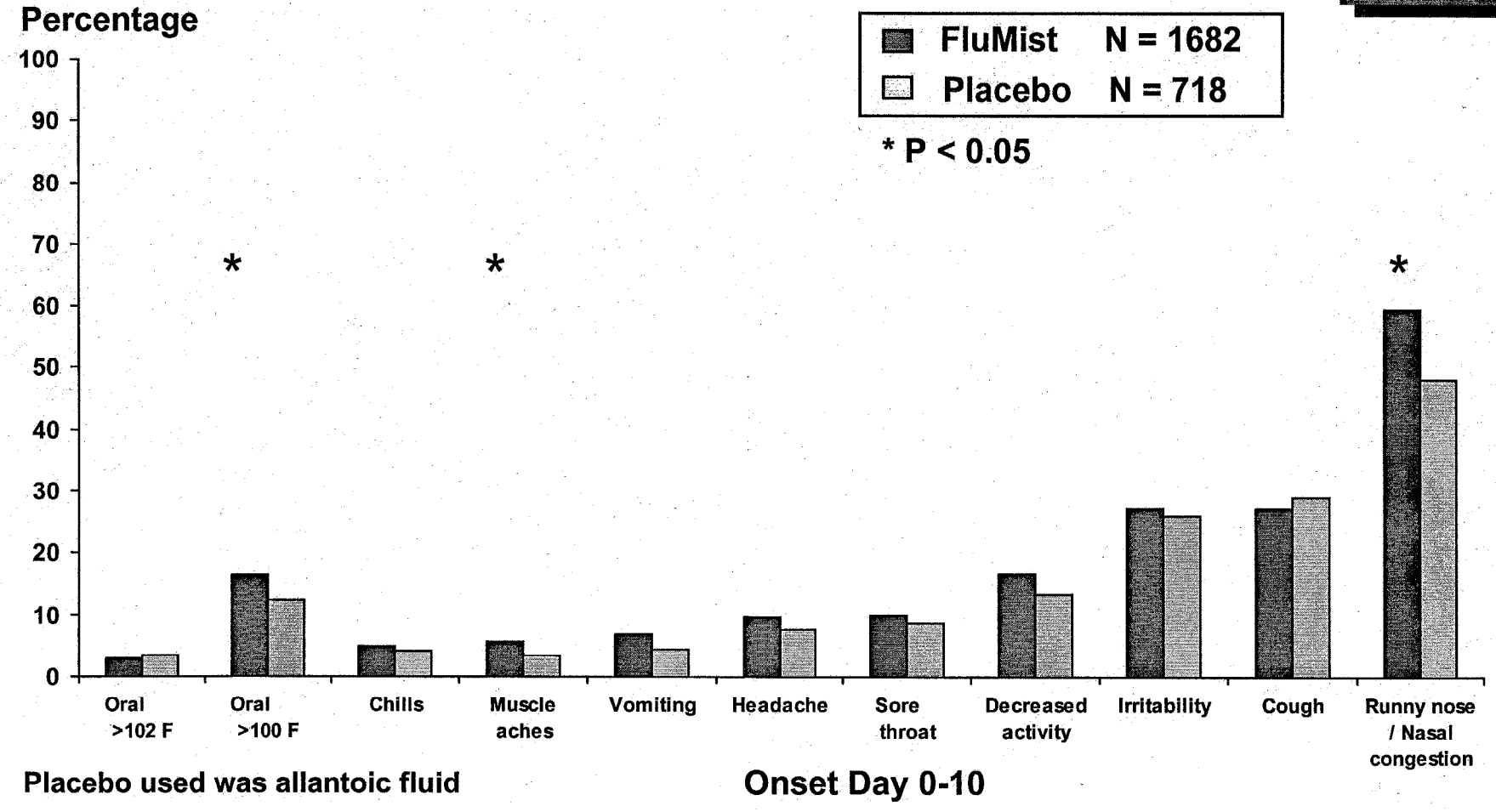
# Vaccine Related Serious Adverse Events

Healthy Children Age 1-17

- Two in vaccinees
  - Wheezing (Day 6 following Dose Two)
  - Bronchiolitis (Day 21 following Dose Two)
- Two in placebo recipients in
  - Laryngitis (Day 3 following Dose One)
  - Croup (Day 4 following Dose One)

# Children with Reactogenicity Events Following Dose One

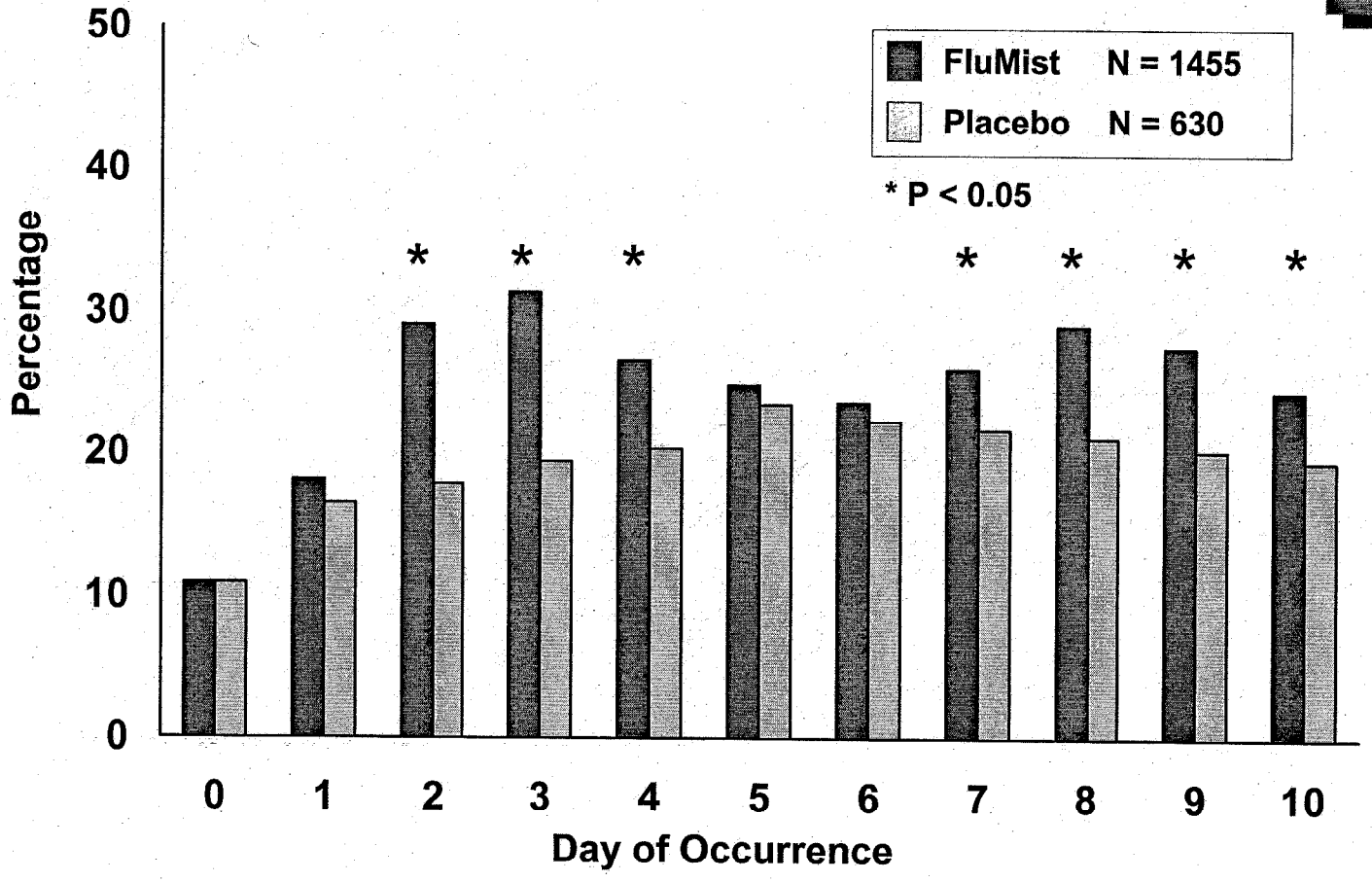
**Placebo Controlled Trials Age 1-8**




**Conclusion: Three events were significantly increased after Dose One**

# Children with Runny Nose / Nasal Congestion Following Dose One Day of Occurrence Analysis

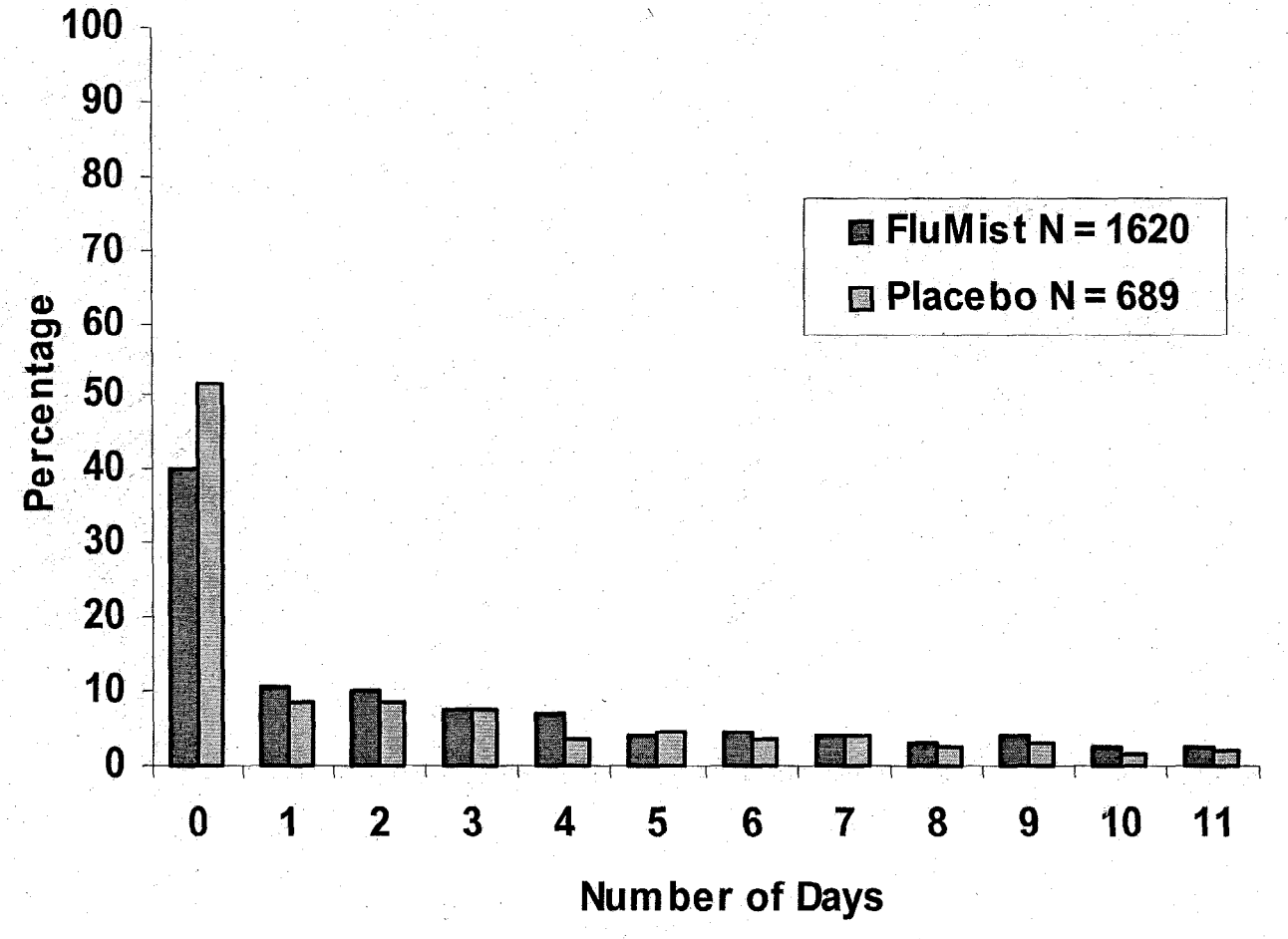
**Placebo Controlled Trials Age 1-8**




**Conclusion: Runny nose/nasal congestion was significantly increased on multiple days after Dose One**

# Number of Days of Runny Nose/Nasal Congestion During the 10-Day Reactogenicity Period Post-Dose One

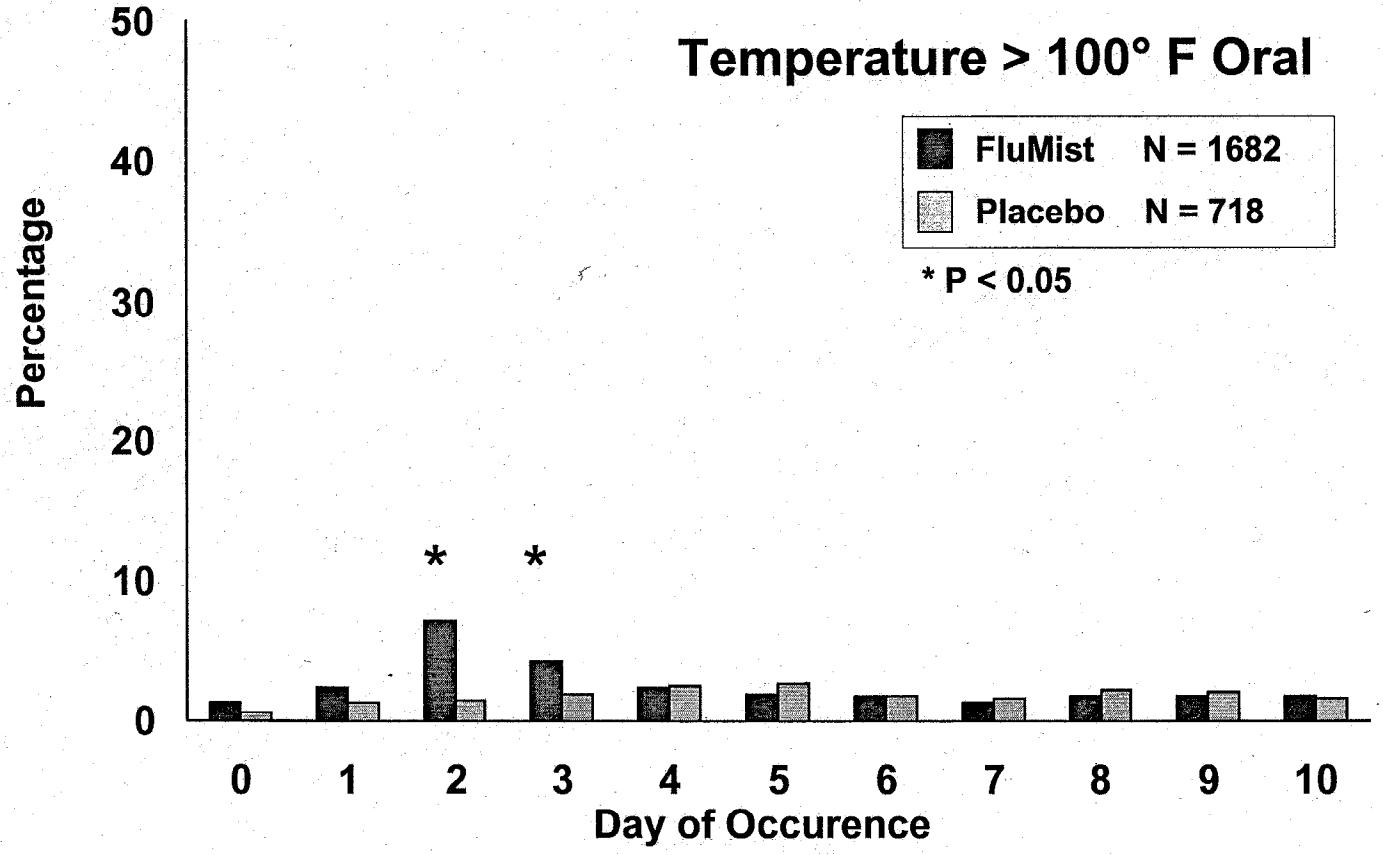
**Placebo Controlled Trials Age 1-8**




**Conclusion:** More placebo recipients than vaccinees had no days of runny nose/nasal congestion.

# Children with Fever Following Dose One Day of Occurrence Analysis

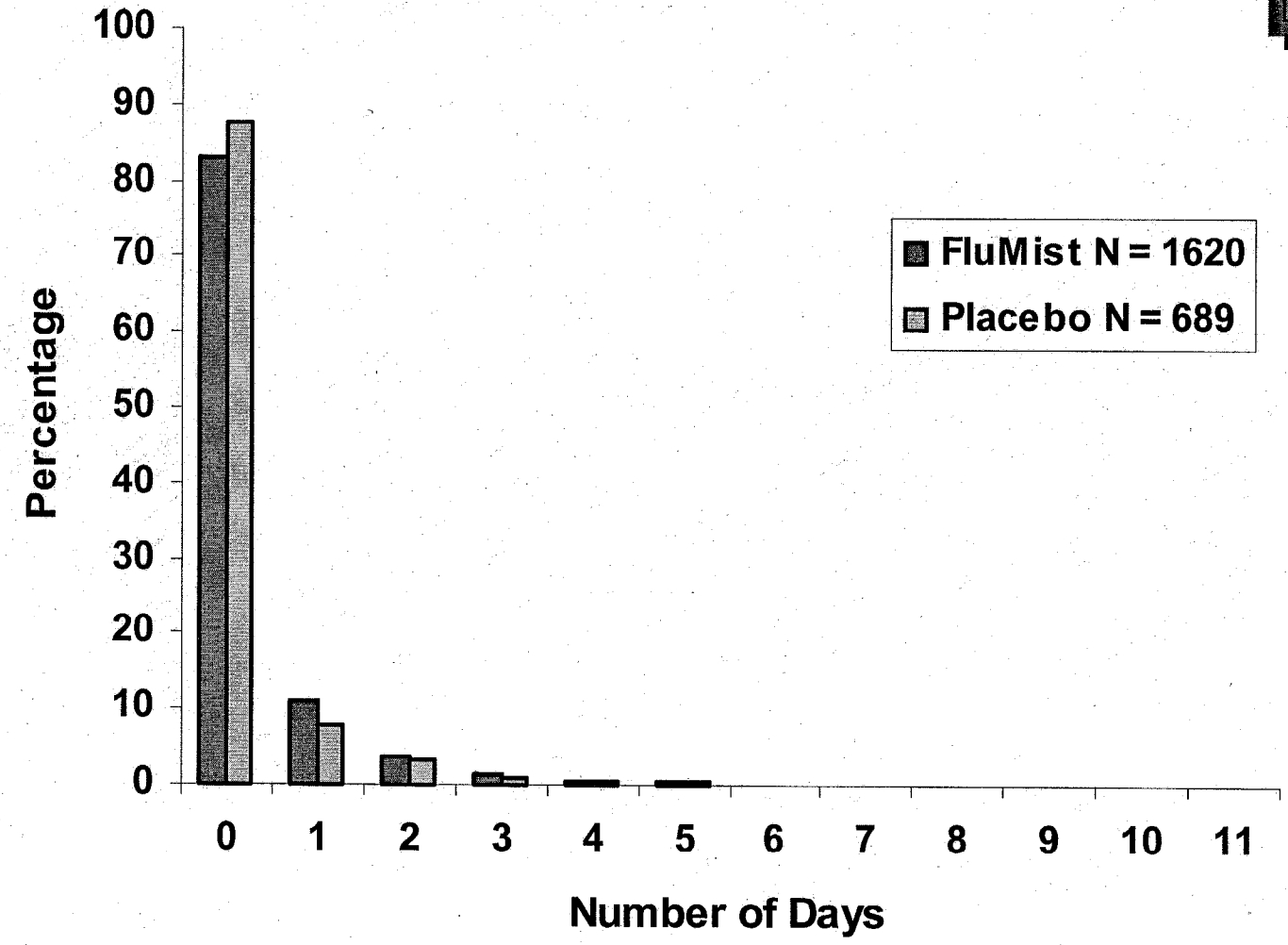
**Placebo Controlled Trials Age 1-8**




**Conclusion: Low grade fever was significantly increased on days 2 and 3 after Dose One**

# Number of Days of Fever > 100°F during the 10-Day Reactogenicity Period Post-Dose One

**Placebo Controlled Trials Age 1-8**




**Conclusion: Most vaccinees had no days of fever > 100° F**

# Healthy Children with Illness During the Reactogenicity Period

**Placebo Controlled Trials Age 1-8**

| Participants with | Dose One | | | Dose Two | | |
|---|---|---|---|---|---|---|
| | FluMist N = 1682 | Placebo N = 718 | P Value | FluMist N = 1379 | Placebo N = 566 | P Value |
| CDC-ILI[a] | 6.9% | 5.7% | 0.42 | 5.9% | 6.9% | 0.60 |
| Temperature > 100° F | 16.5% | 12.3% | 0.02 | 10.6% | 10.1% | 0.78 |
| Temperature > 102° F | 3.1% | 3.5% | 0.49 | 2.2% | 3.5% | 0.14 |
| Temperature > 104° F | 0.1% | 0.1% | 1.00 | 0.3% | 0.5% | 0.50 |

[a] CDC-ILI defined as temperature ≥ 100° F with cough or sore throat events on same day or on consecutive days

All temperatures are oral equivalent

**Conclusions: CDC-ILI was not significantly increased after either dose. Only mild fever was significantly increased after Dose One.**

# Healthy Children with Medication Use During Reactogenicity Period

**Placebo Controlled Trials Age 1-8**

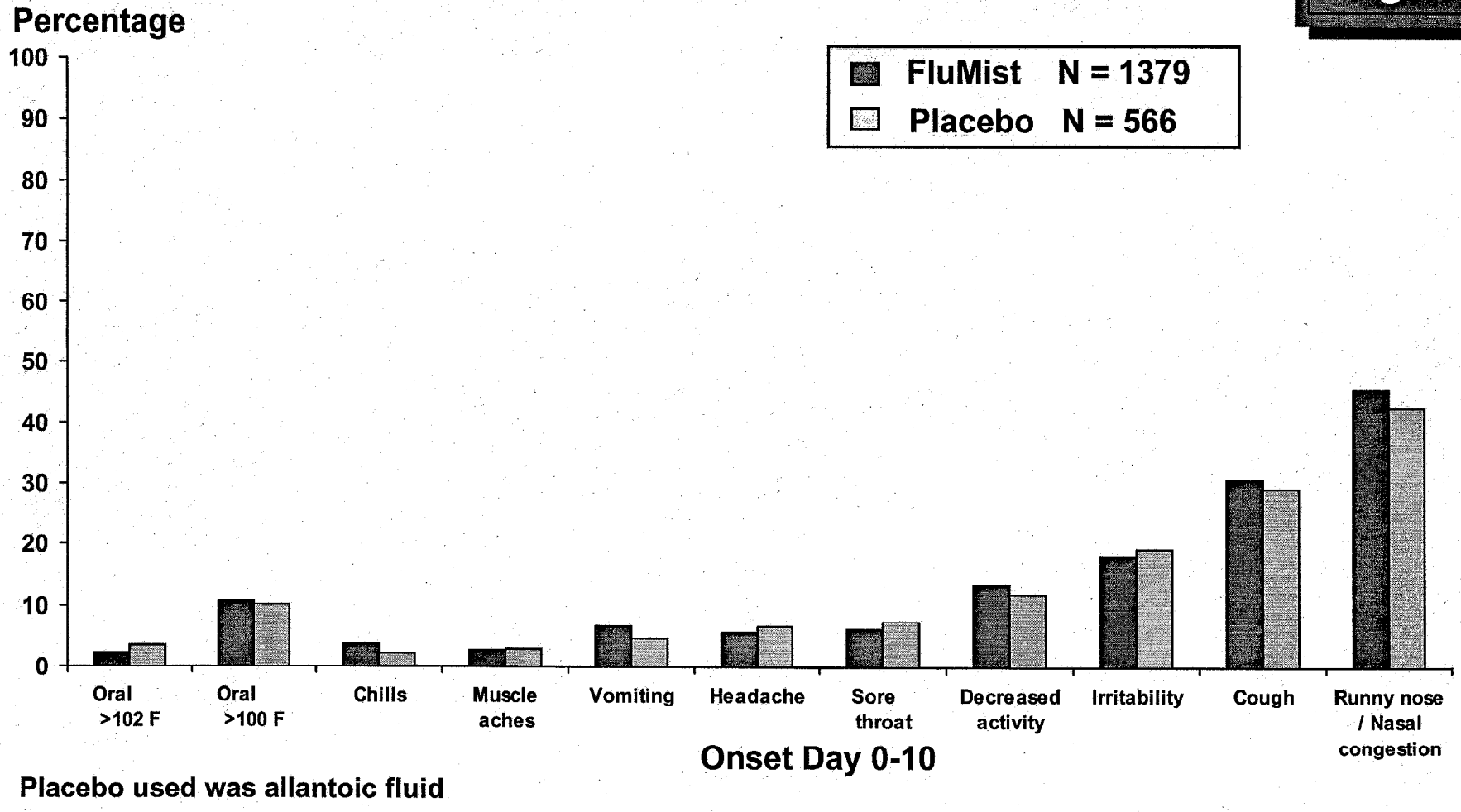
| Medication | Dose One | | | Dose Two | | |
|---|---|---|---|---|---|---|
| | FluMist N = 1704 | Placebo N = 754 | P Value | FluMist N = 1233 | Placebo N = 513 | P Value |
| Antipyretics / analgesics | 21.8% | 16.5% | < 0.01 | 12.5% | 13.5% | 0.64 |
| Antibiotic, oral | 5.2% | 4.1% | 0.26 | 5.9% | 5.1% | 0.57 |
| Antihistamines/ antitussives/ Decongestants | 17.2% | 16.3% | 0.64 | 15.9% | 17.9% | 0.32 |
| Beta Agonist / glucocorticoids (nasal / oral) | .5% | .5% | 1.00 | 1.1% | 0.8% | 0.79 |

* Fisher's Exact test

**Conclusion: Antipyretic/analgesic use was significantly increased after Dose One, but not after Dose Two.**
**No other medication use was significantly increased after either dose.**

# Children with Reactogenicity Events Following Dose Two

**Placebo Controlled Trials Age 1-8**




Placebo used was allantoic fluid

**Conclusion: No events were significantly increased after Dose Two**

# Annual Repetitive Dosing

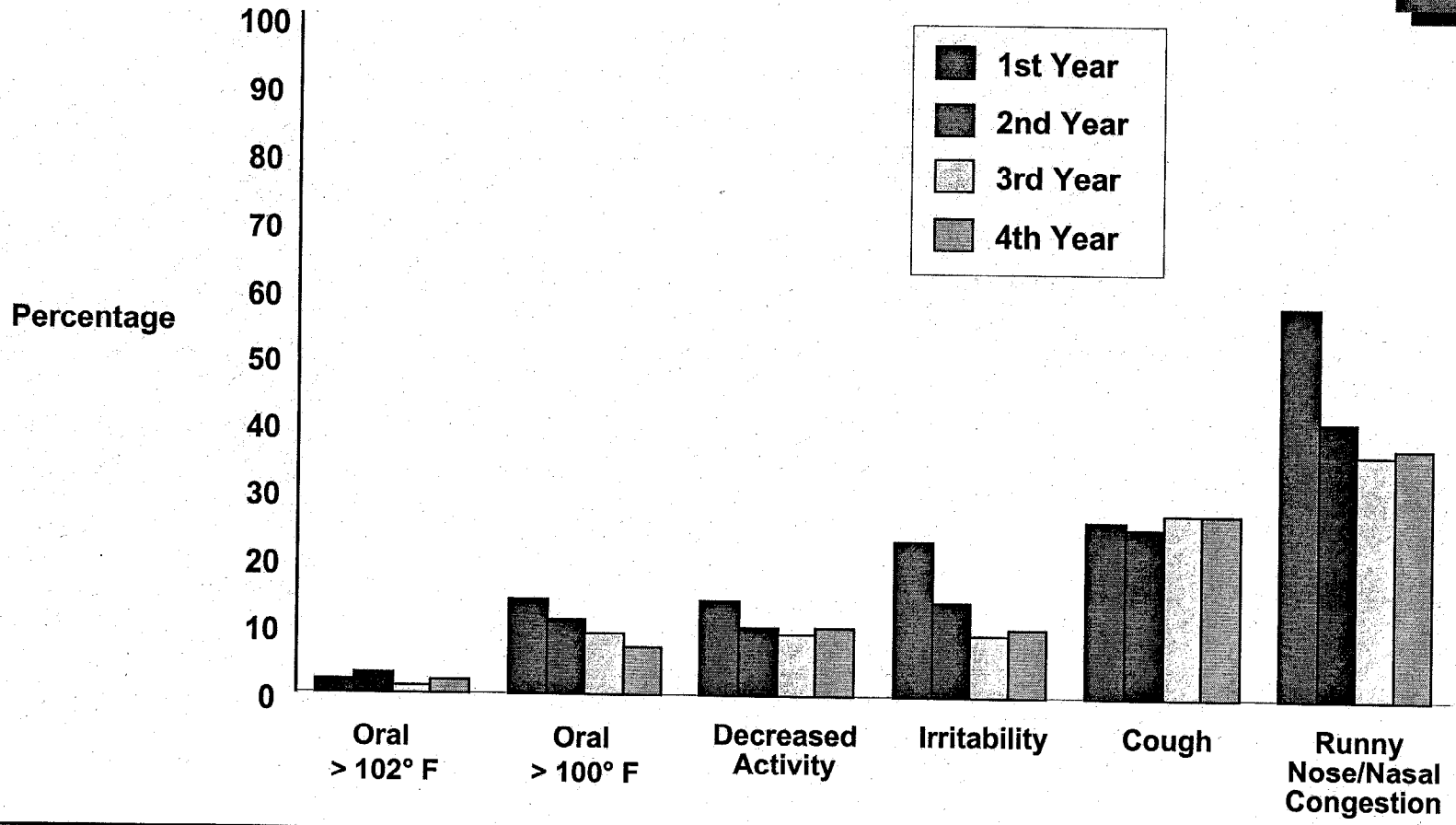
**Healthy Children Age 1-17**

| Season | Number Enrolled | | |
|---|---|---|---|
| | 1 – 8 Years | 9 – 17 Years | Total |
| Second | 2729 | 2042 | 4771 |
| Third | 1219 | 780 | 1999 |
| Fourth | 539 | 10 | 549 |

**Conclusion: Safety profile did not change with repetitive dosing**

# Reactogenicity Events in 549 Children Vaccinated Over Four Consecutive Years

**Healthy Children**




**Conclusion: There was no pattern of increase of reactogenicity events with repetitive dosing**

# Selected Events in Healthy Children During the Reactogenicity Period

**Placebo Controlled Trials Age 1-8**

| Event | Children Ages 1 – 8 Years | | |
|---|---|---|---|
| | FluMist<br>Dose 1 N = 1703<br>Dose 2 N = 1387 | Placebo<br>Dose 1 N = 720<br>Dose 2 N = 570 | P Value |
| | n (%) | n (%) | |
| **Conjunctivitis** | | | |
| Dose 1 | 8 ( 0.5) | 4 ( 0.6) | 1.00 |
| Dose 2 | 7 ( 0.5) | 3 ( 0.5) | 1.00 |
| **Abdominal Pain** | | | |
| Dose 1 | 25 ( 1.5) | 5 ( 0.7) | NC* |
| Dose 2 | 11 ( 0.8) | 2 ( 0.4) | .40 |
| **Lower Respiratory Illness** | | | |
| Dose 1 | 19 ( 1.1) | 7 ( 1.0) | .86 |
| Dose 2 | 15 ( 1.1) | 7 ( 1.2) | 1.00 |
| **Otitis Media** | | | |
| Dose 1 | 27 ( 1.6) | 9 ( 1.3) | .60 |
| Dose 2 | 33 ( 2.4) | 9 ( 1.6) | .22 |

* Significant (P< 0.05 ) in AV006, but not in other studies.

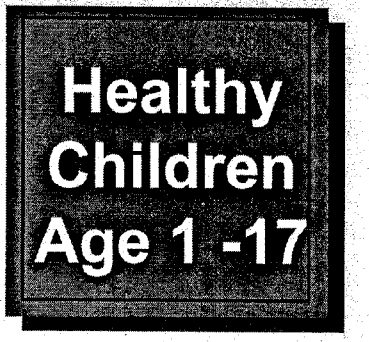
# Abdominal Pain During the Reactogenicity Period

Healthy Children Placebo Controlled Trials

| Characteristics | Dose One | | Dose Two | |
|---|---|---|---|---|
| | FluMist 1665 | Placebo 702 | FluMist 1412 | Placebo 580 |
| Incidence | 25 (1.5%) | 5 (0.7%) | 11 (0.8%) | 2 (0.3%) |
| Age in years Mean | 4.7 | 4.9 | 4.2 | 4.1 |
| Duration in days Mean | 2.9 | 1.8 | 1.3 | 1.0 |
| Number with MD visits | 3 | 0 | 2 | 0 |
| Severity measured in: | 19 of 25 | 1 of 5 | 7 of 11 | 2 of 2 |
| Mild | 16 | 1 | 7 | 2 |
| Moderate | 2 | 0 | 0 | 0 |
| Severe | 1 | 0 | 0 | 0 |

Note: Severity collected in subset of studies.

# Estimated Incidence of Appendicitis in 1-17 Year Olds




| Source | Years | n/N | Estimated incidence per 10,000 person-months |
|---|---|---|---|
| Aviron Trial Data | | | |
| AV019 (Kaiser) (Northern California) | 2000-2001 | 2/6473 | 1.5 |
| | | 1/6473 | 0.8 |
| AV012-Yr 1 (Texas) | 1998-1999 | 0/4257 | 0.0 |
| AV012-Yr 2 (Texas) | 1999-2000 | 1/5153 | 1.4 |
| AV012-Yr 3 (Texas) | 2000-2001 | 3/5073 | 4.3 |
| All Other Trials (multiple) | multiple | 0/5930 | 0.0 |
| Totals, All Aviron Trials | | | |
| 2 AV019 Events + 4 AV012 Events + 0 Events in All Other Trials | | 6/26886 | 1.3 |
| 1 AV019 Events + 4 AV012 Events + 0 Events in All Other Trials | | 5/26886 | 1.1 |
| 0 AV019 Events + 4 AV012 Events + 0 Events in All Other Trials | | 4/26886 | 0.9 |
| | | | |
| Published and Local Data | | | |
| NHDS (USA) | 1996-1999 | | 0.9 |
| Addiss et al. (NHDS) (USA) | 1979-1984 | | 1.2 |
| Luckmann et al. (California) | 1983-1986 | | 1.1 |
| Kaiser (Northern California) | 1995-1999 | | 0.9 |
| Scott & White Temple, Texas | 2000-2001 | | 0.6 |

# Pneumonia Cases Reported within 42 Days of Vaccination in AV006

AV006 Years One and Two

| | Year One | | | | Year Two | |
|---|---|---|---|---|---|---|
| | Dose One | | Dose Two | | Dose One | |
| Pneumonia | FluMist | Placebo | FluMist | Placebo | FluMist | Placebo |
| | N = 1070<br>n (%) | N = 532<br>n (%) | N = 854<br>n (%) | N = 418<br>n (%) | N = 917<br>n (%) | N = 441<br>n (%) |
| Reported in Days 0 – 10 | 4 ( 0.4 ) | 0 ( 0 ) | 0 ( 0 ) | 1 ( 0.2 ) | 0 | 0 |
| Reported in Days 11 – 42 | 8 ( 0.7 ) | 3 ( 0.6 ) | 3 ( 0.4 ) | 2 ( 0.5 ) | 0 | 0 |
| Total Cases | 12 ( 1.1 ) | 3 ( 0.6 ) | 3 ( 0.4 ) | 3 ( 0.7 ) | 0 | 0 |

**Note: No statistical differences were observed**

# Pneumonia

## All Utilization Settings, 1-17 Years of Age, Combined Doses

**Healthy Children AV019**

| FluMist Rate n/N = 14/6473 | Placebo Rate n/N = 10/3216 | Binomial Relative Risk (90% CI) P value |
|---|---|---|
| 1.52 cases / 1000 person-months | 2.18 cases / 1000 person-months | 0.70 (0.35, 1.41) P = 0.39 |

# Daycare Transmission Trial

Children in Daycare

- Children 8 to 36 months of age in Finland
- Double-blind, placebo-controlled
- Randomized 1:1
  - 98 received FluMist
  - 99 received placebo
- Nasal cultures were obtained three times per week for three weeks

# Daycare Transmission Trial Results

Children in Daycare

- 80% of vaccinees shed vaccine virus
- One placebo recipient shed type B vaccine virus on a single day in the 21 day follow up period
  - Symptoms were similar to other participants
  - Vaccine virus retained the *ca* and *ts* phenotype
- Transmission attack rate:
  - 1.75% (one sided UB of the 95% CI: 8%)
- Transmission probability :
  - 0.9% (UB: 2.7%)(MLE using Reed - Frost Model)

# Safety Conclusions

Healthy Children

- FluMist was safe and well-tolerated in children 1 - 17 years of age
- 30,067 doses have been administered to 18,390 healthy children
- Mild, self-limited reactogenicity events observed
- Low risk of other adverse events